# EXHIBIT 108

# Asbestos: Selected Cancers

Committee on Asbestos: Selected Health Effects
Board on Population Health and Public Health Practices

INSTITUTE OF MEDICINE
*OF THE NATIONAL ACADEMIES*

THE NATIONAL ACADEMIES PRESS
Washington, D.C.
**www.nap.edu**

# Executive Summary

## INTRODUCTION

The use of asbestos in many products surged during the 20th century, and asbestos exposure continues despite a sharp reduction in production since the 1980s. Asbestos is an established cause of mesothelioma, an uncommon cancer that arises in the mesothelial cells lining the chest and abdominal cavities, and of lung cancer. It also causes non-malignant respiratory diseases, including asbestosis, a fibrotic disorder of the lung. In addition, the findings of some epidemiologic studies of asbestos-exposed workers have suggested that exposure to asbestos may increase risk of other cancers. This Institute of Medicine committee was charged with evaluating the evidence relevant to the causation of cancers of the pharynx, larynx, esophagus, stomach, and colon and rectum by asbestos and with judging whether the evidence is sufficient to infer a causal association. The specific charge follows:

> The Institute of Medicine's (IOM) Board on Population Health and Public Health Practices will oversee a study that will comprehensively review, evaluate, and summarize the peer-reviewed scientific and medical literature regarding the association between asbestos and colorectal, laryngeal, esophageal, pharyngeal, and stomach cancers. Based on its examination and evaluation of the extant literature and other information it may obtain in the course of the study, the committee will determine if there is a causal association between asbestos and colorectal, laryngeal, esophageal, pharyngeal, or stomach cancers.

The committee's charge was drawn directly from Senate Bill 852, the Fairness in Asbestos Injury Resolution (FAIR) Act.

## COMMITTEE APPROACH

To address the charge, a multidisciplinary committee was appointed by IOM that included experts in biostatistics, epidemiology, mineralogy, oncology, toxicology, and cancer biology. The committee interpreted its charge as requiring a comprehensive and systematic

The committee found several bases for considering that asbestos could plausibly cause laryngeal cancer. The larynx, like the lung, is anatomically in the direct path of inhaled asbestos fibers. Inflammation or damage to the vocal cords could disrupt laminar airflow and predispose to the deposition and accumulation of asbestos fibers in the larynx. Squamous-cell carcinomas of the lung and larynx exhibit certain histologic and clinical similarities; cancers at both sites arise from the respiratory epithelium in regions of squamous metaplasia and dysplasia. Tobacco-smoking is the most important risk factor for both sites, and asbestos exposure is an established cause of lung cancer. Tobacco-smoking may lead to laryngeal damage and increased potential for asbestos fibers to deposit in the trachea. Alcohol consumption is also a recognized risk factor for laryngeal cancer, with heavy consumption synergizing markedly with smoking. Together with smoking and drinking, accumulation of asbestos fibers could produce chronic irritation or inflammation, accelerating the progression of neoplasia. However, no clinical data document the accumulation and persistence of asbestos fibers in the larynx, and there is a lack of experimental support from animal studies.

Considering all the evidence, the committee placed greater weight on the consistency of the epidemiologic studies and the biologic plausibility of the hypothesis than on the lack of confirmatory evidence from animal studies or documentation of fiber persistence in the larynx. *The committee concluded that the evidence is **sufficient** to infer a causal relationship between asbestos exposure and laryngeal cancer.*

### Esophageal Cancer

Both case-control and cohort studies of esophageal cancer were reviewed, but the available body of evidence was limited. Only three case-control studies met the criteria for inclusion, so there were too few for meta-analysis. There were more cohort populations with relevant results, although the number of cases was often small. The mortality studies did not distinguish between histologic subtypes; if there were specific asbestos-subtype associations, the overall grouping of esophageal cancers would tend to obscure them. In assessing biologic plausibility, the histologic type of cancer, potential dose to the target tissues, and possible mechanisms were considered.

The three case-control studies did not have consistent results, and the number of exposed cases was generally small. Two incorporated adjustment for tobacco-smoking and alcohol consumption. One observed a small excess risk but did not find evidence of a dose-response relationship, and the other found no evidence of an excess. A third, older study found an excess, but it was based on a single case, and so was difficult to interpret. Few cohort studies presented data explicitly on esophageal cancer, because of the rarity of the disease, and their statistical precision was often low. The results for the 25 cohort populations with information on esophageal cancer were mixed. The summary RR computed from the cohort studies was 0.99 (95% CI 0.78-1.27). Although some studies did observe excess risks, overall there was little consistency in the epidemiologic data. Six animal-feeding studies did not find an association with esophageal cancer, and there is no other experimental evidence that asbestos fibers act as a direct or indirect carcinogen specifically in the esophagus.

Some studies have found an association between asbestos exposure and esophageal cancer, but the overall results of epidemiologic studies are mixed. In addition, what little evidence there is from animal experiments about asbestos's carcinogenic potential specifically on esophageal tissues does not support biological activity at this site. *The committee concluded that the evidence is **inadequate** to infer the presence or absence of a causal relationship between asbestos exposure and esophageal cancer.*

### Stomach Cancer

In its final dataset, the committee considered 42 occupational cohorts and five population-based case-control studies that provided data on stomach cancer risk. Overall, the occupational cohorts consistently, although not uniformly, suggested risks increased above risks in the general population (RR=1.17, 95% CI 1.07-1.28). The results of case-control studies were less consistent (RR=1.11, 95% CI 0.76-1.64), and suggested neither increased nor lower-than-expected risks associated with asbestos. Considering just the cohort studies, the committee noted that observed risk increases were modest. There were also somewhat consistent patterns supportive of dose-response relations, although trends were not especially strong. Six lifetime feeding studies of asbestos in rodents provided no evidence that asbestos fibers act as a direct or indirect carcinogen in the stomach.

The most frequent histologic type of stomach cancer in western countries is adenocarcinoma, which is most commonly associated with *Helicobacter pylori* infection and inflammation. Tobacco-smoking is also a risk factor for stomach adenocarcinoma. The potential role of asbestos fibers as a cofactor with established risk factors has not been investigated experimentally or epidemiologically. Asbestos bodies have been identified in the stomach and in other sites in the gastrointestinal tract and in other organs. The possibility that asbestos fibers could accumulate at sites of mucosal injury and ulceration has not been explored. There is no experimental evidence from animal toxicology studies that asbestos fibers act as a direct or indirect carcinogen in the stomach.

Overall, the epidemiologic studies revealed fairly modest risk increases and somewhat fragmentary evidence of a dose-response relationship. Animal experimentation has not provided supportive evidence of causation, although the potential for asbestos fibers to accumulate at sites of stomach mucosal injury lends some mechanistic support to potential carcinogenesis. *The committee concluded that the evidence is **suggestive but not sufficient** to infer a causal relationship between asbestos exposure and stomach cancer.*

### Colorectal Cancer

The committee evaluated the overall evidence on colorectal cancer because its charge addressed cancers of the colon and rectum together. The evidence thus included studies providing information on the two sites separately and studies reporting on colorectal cancer overall. Case-control studies of colon or rectal cancers included four studies in which the two outcomes were considered in a single category of colorectal cancer, six studies of only colon

cancer, and one of only rectal cancer. In addition, 41 occupational cohorts were reviewed, almost all of which had the necessary information to derive a combined risk estimate for colon and rectal cancers.

There was some inconsistency among the 13 RRs reported from the case-control studies (aggregate RR=1.16, 95% CI 0.90-1.49), and findings from many of the studies were inconclusive. Although most of the estimated RRs were greater than 1, two of the studies had lower estimated risks for those exposed to asbestos. The case-control study with the most detailed assessment and analysis of asbestos exposure did not find an association between exposure to asbestos and the risk of colorectal cancer. In contrast, the occupational-cohort studies more consistently, although not uniformly, suggested increased risks of colorectal cancer in exposed people than in the general population (RR=1.15, 95% CI 1.01-1.31).

The summary estimate of association from the case-control studies was similar to that from the cohort studies, but the CI was wider, and evidence of a dose-response relationship in the case-control studies was lacking. The overall observed risk estimate from cohort studies was modestly increased, although it had 95% CI that just excluded 1.0 and some evidence of a dose-response relationship.

There was only limited information available relevant to biologic plausibility. Colorectal tumors in humans are most commonly adenocarcinomas that arise in polyps. Multiple risk factors are associated with colon cancer, including familial predisposition, age, obesity, physical inactivity, and inflammatory bowel disease. The potential role of asbestos fibers as a cofactor has not been investigated in epidemiologic or experimental studies. Asbestos bodies and asbestos fibers have been identified in the colon, including for a small cohort of asbestos workers who had colon cancer. Animal models have failed to produce colon or colorectal cancer even studies that involved high-dose feeding of asbestos to rodents. However, studies employing high-dose feeding of chrysotile asbestos to rats did produce benign adenomatous colonic polyps, a precursor to the most common form of colon cancer in humans.

The committee concluded that the evidence is **suggestive but not sufficient** to infer a causal relationship between asbestos exposure and colorectal cancer.

## CLOSING COMMENTS

The committee was charged with reviewing evidence on a widely used material that is known to cause respiratory malignancy. Asbestos has been extensively investigated, epidemiologically and experimentally, as a cause of mesothelioma and lung cancer. However, its potential to cause malignancy at other sites that may also receive a substantial dose of asbestos fibers has not been as extensively investigated.

The committee considered the existing evidence from in vitro and animal experimentation to gain an understanding of mechanisms of carcinogenesis that might plausibly apply to the tissues in question and to determine the extent of toxicologic support for the development of cancers at the specified sites following asbestos exposure. Much of the information reviewed by the committee came from cohort studies of workers that focused on

investigating respiratory effects and that reported information on risks of other diseases, including the cancers covered by this committee's charge, only incidentally. Other evidence came from case-control studies that were directed at the causes of the cancers of interest but that were not specifically designed to address asbestos exposure, and their exposure assessments were of varied quality.

Table ES.1 provides a distillation of the committee's findings about whether asbestos is a causal factor for cancers at the five sites indicated for evaluation in the committee's charge and the FAIR legislation.

The committee's review identified limitations of the available evidence and the resulting uncertainty in its conclusions. Although the committee was not charged with developing a research agenda to address the information gaps, its review indicated many research needs. Studies directed at doses of fibers received by organs other than the lung are needed; mechanistic studies directed at these organs could be a useful complement to work on respiratory carcinogenesis by asbestos fibers. Studies involving animal models with high risk of cancer at the designated sites might also be considered. Consideration should be given to approaches to strengthen the epidemiologic information on asbestos exposure and risk of cancer at the sites in the committee's charge. Information might be gained from further follow-up of some of the cohorts of asbestos-exposed workers; however, the committee is concerned that further study of these cohorts maybe impossible because most were initiated decades ago and their records may not have been maintained. Some effort might be made to determine whether key cohorts could be followed up or new studies on potentially informative populations started.

[INSERT TABLE ES. 1]

[END OF EXECUTIVE SUMMARY]

**TABLE ES.1** Causal association between specified cancer and asbestos

| Cancer | Evidence for presence or absence of causal relationship to asbestos |
|---|---|
| Laryngeal | Sufficient |
| Pharyngeal | Suggestive but not sufficient |
| Stomach | Suggestive but not sufficient |
| Colorectal | Suggestive but not sufficient |
| Esophageal | Inadequate |